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(54) Title: ANTI-INFLAMMATORY AGENTS

(57) Abstract: The invention relates to the use of mitochondrial K_{ATP} channel openers, particularly compounds of general formula (I), for the treatment or prevention of inflammation by inducing apoptosis or inflammatory cells.

BNSDOCID: <WO 02400025A1 >

ANTI-INFLAMMATORY AGENTS

Technical field

The present invention relates to the use of mitochondrial K_{ATP} channel openers, such as compounds of general formula (I), for the treatment or prevention of inflammation.

Background of the invention

Inflammation is caused by the emigration of inflammatory cells such as neutrophils, T-lymphocytes and eosinophils into the tissues, where they are activated. The inflammatory cells are likely to live longer at the site of inflammation due to growth factors and inflammatory mediators produced by the various cells. For instance in bronchial asthma a massive eosinophilia is present. Eosinophils contain cytotoxic granules in their cytoplasm and eosinophil activation/degranulation (lysis) seems to result in epithelial cell damage and airway hyperresponsiveness. Eosinophil survival is prolonged by growth factors such as IL-5 and GM-CSF, which inhibit eosinophil apoptosis. Apoptosis is a physiological process of programmed cell death distinct from pathological necrosis. In apoptosis the granule contents of eosinophils are removed without harmfull effects characteristic of necrosis (i.e. inflammation and tissue damage).

Apoptosis is chararterised by specific biochemical and morphological changes including cell shrinkage, which may involve K^+ efflux, surface blebbing, chromatin condensation and endonuclease-catalyzed DNA fragmentation. Mitochondria are likely to have an important role in regulating apoptotic mechanisms. The evidence is based on the fact that mitochondria contain various proteins that can activate the apoptotic process e.g caspases, cytochrome c, apoptosis inducing factor (AIF). Currently it is believed that a decrease in mitochondrial membrane potential followed by cell shrinkage and generation of reactive oxygen species precede nuclear alterations detected in apoptotic cells.

Agents which are able to open mitochondrial K_{ATP} channels (mitochondrial ATP dependent potassium channels) have been shown to induce mitochondria swelling by lowering the mitochondrial membrane potential (Szewczyk, A. and Marban, E., Trends Pharmacol Sci (1999) 20:157-161). The reduced membrane

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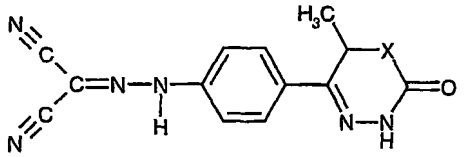
potential leads to opening of the mitochondrial permeability transition pore leading to volume dysregulation, which may finally cause mitochondrial membrane rupture.

Compounds of general formula (I)



(I)

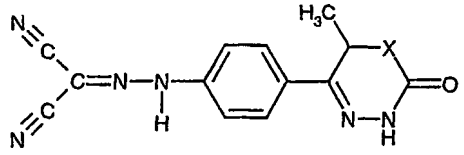
where X is C or S, have been described in applicant's European Patent No. 383449 B1. The compounds sensitize troponin-C in the heart muscle cells to calcium and are useful in the treatment of congestive heart failure.

The compound of formula (I), where X is C, is simendan or [[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile. Its optically active enantiomers have been described in applicant's European Patent No. 565546 B1. It was shown that the cardiotonic effects were predominantly due to the (-)-enantiomer of compound (I), i.e. levosimendan.

The effect of simendan to reduce infarct size and arrhythmias has been disclosed in WO 93/21921. It was also shown that the both enantiomers of simendan reduced arrhythmias, and that the (+) enantiomer increased survival. The use of levosimendan for the treatment of pulmonary hypertension has been disclosed in WO 99/66912.

Summary of the invention

It has been found that compounds of formula (I)



(I)

where X is C or S, and optically active enantiomers thereof are capable of opening mitochondrial K_{ATP} channels and inducing apoptosis of inflammatory cells. Therefore, the compounds are useful in the treatment or prevention of various inflammatory conditions.

Accordingly, the present invention provides a new medical use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment or prevention of inflammation.

The present invention also provides use of a mitochondrial K_{ATP} channel opening agent in the manufacture of a medicament for use in the treatment or prevention of inflammation.

The present invention also provides a method for the treatment or prevention of inflammation in a patient, which method comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The present invention also provides a method for the treatment or prevention of inflammation in a patient, which method comprises administering to a patient in need thereof a therapeutically effective amount of a mitochondrial K_{ATP} channel opening agent.

Furthermore, the present invention provides optically substantially pure (+) enantiomer of compound of formula (I) where X is S, as well as pharmaceutical compositions thereof, such compound and compositions being useful in the treatment or prevention of inflammation.

The inflammation to be treated or prevented according to the present invention is in particular inflammation of the airways associated with bronchial asthma the treatment being independent of bronchodilatation. Other inflammations suitable to be treated or prevented according to the present invention include e.g. rhinitis, myocarditis, inflammatory bowel disease, arthritis, rheumatoid arthritis and inflammation in muscular tissue.

Compounds of formula (I) are preferred agents for the treatment or prevention of inflammation according to the invention. Optically active (+) enantiomers (dextro forms) of the compounds of formula (I) are particularly preferred.

Examples of compounds of formula (I) are:
[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono]propanedinitrile (simendan) and
[[4-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)phenyl]hydrazono]propanedinitrile (compound (I) where X is S).

FIG. 1a shows the effect of compound A (μM) on constitutive (medium) and

Fas-induced human eosinophil apoptosis and on reversal of IL-5-afforded eosinophil survival during 40 h in culture.

FIG. 1b shows the effect of compound B (μM) on constitutive (medium) and Fas-induced human eosinophil apoptosis and on reversal of IL-5-afforded eosinophil survival during 40 h in culture.

FIG. 2 shows the effect of levosimendan and dextrosimendan (μM) on membrane potential ($\Delta\Psi$) of rat liver mitochondria respiring only on endogenous substrates in KCl medium.

FIG. 3a shows the effect of levosimendan on carrageenan (1 mg)-induced rat paw edema. The vertical bars indicate SEM. * $p<0.05$, anova and Dunnett's test, n = 9-10.

FIG. 3b shows the effect of dextrosimendan on carrageenan (2 mg)-induced rat paw edema. The vertical bars indicate SEM. * $p<0.05$, ** $p<0.01$, Student's t-test, n = 9-10, except 10 mg/kg and control, n = 20.

Detailed description of the invention

The term "mitochondrial K_{ATP} channel opening agent" means here a pharmaceutically acceptable compound, which is capable to open mitochondrial ATP dependent potassium channel in a mammal, including a human. The mitochondrial K_{ATP} channel opening activity of a compound can be demonstrated by measuring the decrease of the membrane potential of isolated mitochondria. The method is illustrated in detail in Example 2. Positive result in the test demonstrates a potential usefulness of the compound in the method of the invention.

Mitochondrial K_{ATP} channel opening agents suitable for use in the method of the invention include, but are not limited to compounds of formula (I). In general, any pharmaceutically acceptable mitochondrial K_{ATP} channel opening agent, including those well known in the art, can be used in the method of the invention. Preferably, the mitochondrial K_{ATP} channel opening agent is selective to the mitochondrial K_{ATP} channel over other K channels.

Compounds of formula (I) can be prepared as described in EP 383449 B1 by treating the corresponding amino intermediates with sodium nitrite and malononitrile. Optically active enantiomers of the compounds (I) can be prepared similarly

using the optically active amino intermediates as described in EP 565546 B1. Optically substantially pure (+) enantiomers (dextro forms) of the compounds (I) are particularly preferred, since they are devoid of significant hemodynamic effects. The term "optically substantially pure" means here optical purity over about 90 %, preferably over 95 % and more preferably over 99 %. Salts of the compound of the invention can be prepared by known methods. Pharmaceutically acceptable salts are useful as active medicaments, however, preferred are the salts with alkali or alkaline earth metals.

The compound of the invention may be administered in a variety of ways including orally, parenterally, transdermally or by inhalation using conventional forms of preparations, such as capsules, tablets, granules, powders, suppositories, injections, patches, suspensions and syrups. The term "effective amount" means an inflammation inhibiting or preventing amount of compound of the invention. The compound of the invention may be administered periodically or daily or several times a day depending upon the patient's needs. The administration may be systemic or local. The daily dosage may vary depending on the compound to be administered, the age and body weight of the patient, the condition to be treated as well as on the administration method. For example, the compounds of formula (I) may be administered orally to man in daily dose within the range of from about 0.1 mg to about 100 mg, preferably from about 0.5 to about 50 mg. The compounds of the invention may be administered alone or together with other active compounds.

The compositions for the active ingredients can be prepared by the methods commonly employed in the art. In addition to the active compound the compositions may contain pharmaceutically acceptable additives commonly used in the art, such as carriers, binders, excipients, lubricants, suspending agents and diluents. The amount of the active compound in the compositions of the invention is sufficient to produce the desired therapeutic effect, for example, for a compound of formula (I), about 0.1 mg to 100 mg, more preferably from about 0.5 to about 50 mg, in unit dosage for oral, pulmonary or parenteral administration.

Example 1. Apoptosis of eosinophils

Apoptosis was determined in eosinophils isolated from the peripheral blood of apparently healthy volunteers. White blood cells were obtained from whole blood by sedimentation with 3% hydroxyethyl starch, layered on Ficoll and centrifuged. Contaminating red blood cells were lysed by hypotonic treatment. Eosinophils were purified from neutrophils using immunomagnetic anti-CD16 antibody conjugated

beads. The obtained eosinophils were cultured for 22 – 40 h in RPMI 1640 medium supplemented with 10% fetal calf serum plus antibiotics.

Eosinophil apoptosis was determined by propidium iodide staining of DNA fragmentation and flow cytometry and confirmed by morphological analysis. Apoptosis index is expressed as (number of apoptotic cells / number of total cells).

The effects of compounds A and B were studied:

A. (+)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-hydrazono]propanedinitrile (dextrosimendan) and

B. (+)-[[4-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)phenyl]hydrazono]propanedinitrile

The results are shown in Fig. 1a and 1b. It can be seen that both compounds dose-dependently enhanced constitutive (medium) and Fas- induced human eosinophil apoptosis and reversed IL-5-afforded eosinophil survival during 40 h in culture.

Example 2. Mitochondrial ATP dependent potassium channel opening

In respiring mitochondria, the decrease in $\Delta\Psi$ due to the K_{ATP} channel opening is compensated by an increased respiration rate. When mitochondria respires only on endogenous substrates, and phosphorylation is blocked by oligomycin, the respiration rate is sufficient to generate a high $\Delta\Psi$. However, opening of K_{ATP} channels leads to a decrease in $\Delta\Psi$, which could not be compensated by increased respiration rate. In such a model, opening of K_{ATP} channel is unmasked, and can be recorded. This model was applied to test if opening could be induced by dextrosimendan and levosimendan.

Mitochondria were isolated from rat livers by differential centrifugation in medium containing 210 mM mannitol, 70 mM sucrose, 10 mM Hepes,1 mM EGTA and 5 mg/ml bovine serum albumin, pH 7.4. The mitochondrial protein concentration was determined by modified Biuret method. Oxygen consumption of isolated liver mitochondria was recorded at 25°C by means of the Clark-type electrode system in the KCl medium (100 mM KCl, 2 mM KH_2PO_4, 10 mM HEPES, 1 mM $MgCl_2$, pH 7.4 with TRIZMA base) or choline chloride medium (100 mM choline chloride, 2 mM NaH_2PO_4, 10 mM HEPES, 1 mM $MgCl_2$, pH 7.4 with TRIZMA base). The final mitochondrial protein concentration used in experiments was 1mg protein/ml. For

studies of respiring mitochondria, 5 mM succinate in the presence of 5 μM rotenone was used as substrate.

Membrane potential ($\Delta\Psi$) of liver mitochondria was measured with rhodamine 123 as a fluorescent probe using the excitation at 503 nm and emission at 527 nm at room temperature with the Hitachi F4000 fluorometer. The difference in fluorescence between mitochondria with addition of FCCP (0.4 μM) and without it was taken as 100%, and decrease in membrane potential by the tested compounds was expressed in % of FCCP effect.

Dextrosimendan and levosimendan (< 2.58 μM concentration) decreased the $\Delta\Psi$ of rat liver mitochondria, respiring only on endogenous substrates in KCl medium (supplemented with 400 μM ATP and 1mg oligomycin/mg protein) and did not significantly change $\Delta\Psi$ in the choline chloride medium.

5-hydroxydecanoate (5-HD), the selective blocker of mitochondrial K_{ATP} channel, abolished the effect of dextrosimendan and levosimendan (not shown). These results indicate that the decrease in $\Delta\Psi$ of mitochondria, respiring only on endogenous substrates, by dextrosimendan and levosimendan is due to the mitochondrial K_{ATP} channel opening.

Example 3. Effects on carrageenan-induced paw edema in rats.

The acute inflammation was induced to the male Wistar rats by an injection of 0.1 ml of 1 or 2 % lambda-carrageenan solution into the subplantar tissue of the right hind paw (= 1 or 2 mg/paw). Three hours after the carrageenan injection the rats were killed. Both hind paws were cut off just above the heel and weighed. The test compounds (levosimendan and dextrosimendan) were administered orally 30 minutes before the induction of inflammation using dosing levels:

Levosimendan	0.1, 1 and 10 mg/kg
Dextrosimendan	10, 30 and 100 mg/kg

Control rats were included in each experiment. The difference between the weight of the right and the left hind paw was regarded as swelling. 9-10 animals were included in each group.

The results are shown in Fig. 3a (levosimendan) and 3b (dextrosimendan). It can be seen that both levosimendan and dextrosimendan inhibited the carrageenan-induced rat paw edema significantly.

Example 4. (+)-[[4-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)phenyl]hydrazono]propanedinitrile

a) Resolution of rasemic (±) 5-(4-aminophenyl)-6-methyl-3,6-dihydro-[1,3,4]-thiadiazin-2-one with dibenzoyl-L-tartaric acid

(±) 5-(4-aminophenyl)-6-methyl-3,6-dihydro-[1;3,4]-thiadiazin-2-one (20.4 g, 0.009 mol) was dissolved in acetonitrile (816 ml) upon heating. To this solution dibenzoyl-L-tartaric acid (52.0 g, 0.14 mol) was gradually added. The mixture was stirred upon heating until a clear solution was obtained. The solution was then cooled slowly to room temperature with stirring. After being further stirred for 2 h in room temperature the crystalline product was filtered. The enantiomeric purity of the precipitate was checked by HPLC and the recrystallization was repeated in same conditions until the product had the enantiomeric purity over 99.0 %. The wet salt was then dissolved in water (150 ml) and potassium carbonate solution (190 g K_2CO_3 in 750 ml of water) was added with stirring. The free base was extracted with ethyl acetate, washed with water and evaporated to dryness in vacuo, yielding (+) 5-(4-aminophenyl)-6-methyl-3,6-dihydro-[1,3,4]-thiadiazin-2-one as a crystalline solid (1.34 g) with optical purity 100.0 %, chromatographic purity 99.5 %, m.p. 216-220° C, $[a]_D^{25}$ = +1000 °.

b) Preparation of (+)-[[4-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)phenyl]hydrazono]propanedinitrile

(+) 5-(4-aminophenyl)-6-methyl-3,6-dihydro-[1,3,4]-thiadiazin-2-one (1.34 g, 6 mmol) was dissolved in water (23 ml) and 6 N hydrochloric acid (4.5 ml). The solution was stirred and cooled. A cooled solution of sodiumnitrite (0.5 g) in water (5 ml) was added. Then a cooled solution of malononitrile (0.9 g) in t-butanol (54 ml) was added. In the end to the solution was added a cooled solution of sodium acetate (5.4 g) diluted in water (40 ml). The reaction mixture was stirred under cooling (0° C) for 3 hours. After stirring the crystalline product was filtered and washed with water, yielding (+)-[[4-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)phenyl]hydrazono]propanedinitrile as a crystalline solid (1.7 g) with optical purity of 100 %, chromatografic purity 99.3 %, m.p. 125-128° C, $[a]_D^{25}$ = +1002 °.

Claims

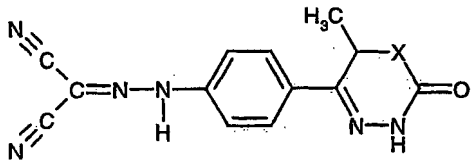
1. Use of a mitochondrial K_{ATP} channel opening agent in the manufacture of a medicament for the treatment or prevention of inflammation.

2. Use according to claim 1, wherein the treatment or prevention of inflammation is achieved by inducing apoptosis of inflammatory cells.

3. Use according to claim 1 or 2, wherein the inflammation to be treated or prevented is inflammation of the airways associated with bronchial asthma.

4. Use according to claim 1 or 2, wherein the inflammation to be treated or prevented is rhinitis, myocarditis, inflammatory bowel disease, arthritis, rheumatoid arthritis or inflammation in muscular tissue.

5. Use of a compound of formula (I)



(I)

wherein X is C or S, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prevention of inflammation.

6. Use according to claim 5, wherein the inflammation to be treated or prevented is inflammation of the airways associated with bronchial asthma.

7. Use according to claim 5, wherein the inflammation to be treated or prevented is rhinitis, myocarditis, inflammatory bowel disease, arthritis, rheumatoid arthritis or inflammation in muscular tissue.

8. Use according to any of claims 5 to 7, wherein the compound of formula (I) is substantially pure (+) enantiomer.

9. Substantially pure (+) enantiomer of [[4-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)phenyl]hydrazono]propanedinitrile.

10. Pharmaceutical composition comprising as an active ingredient substantially pure (+) enantiomer of [[4-(3,6-dihydro-6-methyl-2-oxo-2H-1,3,4-thiadiazin-5-yl)phenyl]hydrazono]propanedinitrile.

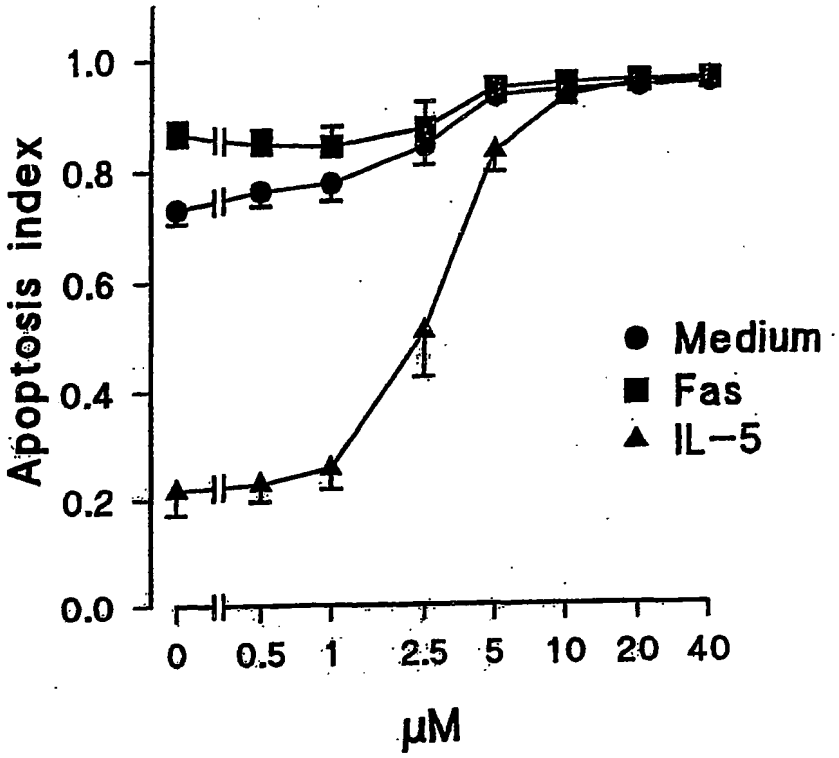
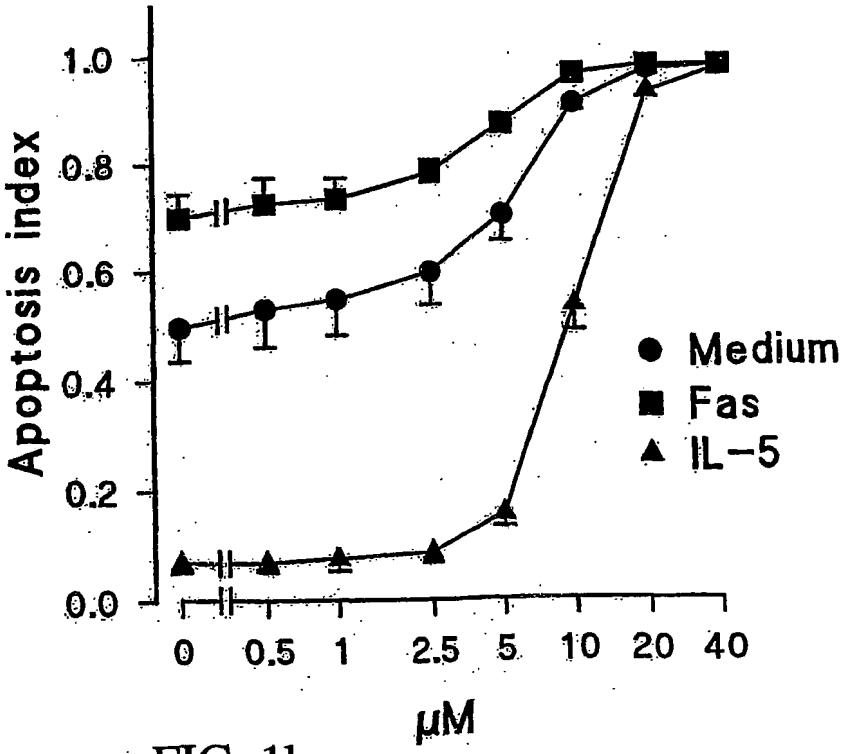

Apoptosis index
1.0
0.8
0.6
0.4
0.2
0.0
0
0.5
1
2.5
5
10
20
40
μM
Medium
Fas
IL-5

FIG. 1a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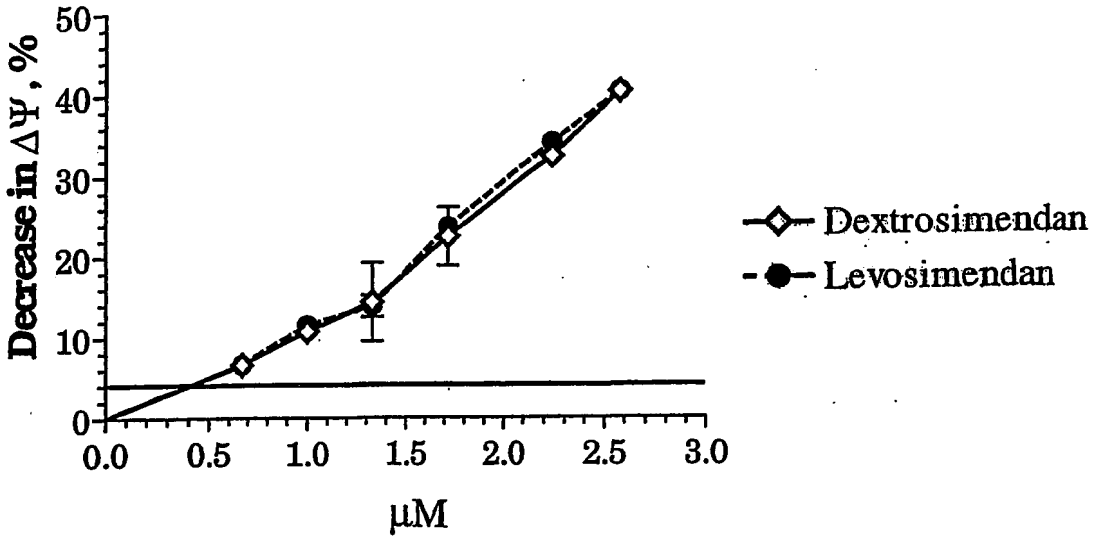
Medium
Fas
IL-5

FIG. 1b


Decrease in ΔΨ, %
50
40
30
20
10
0
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1.0
1.5
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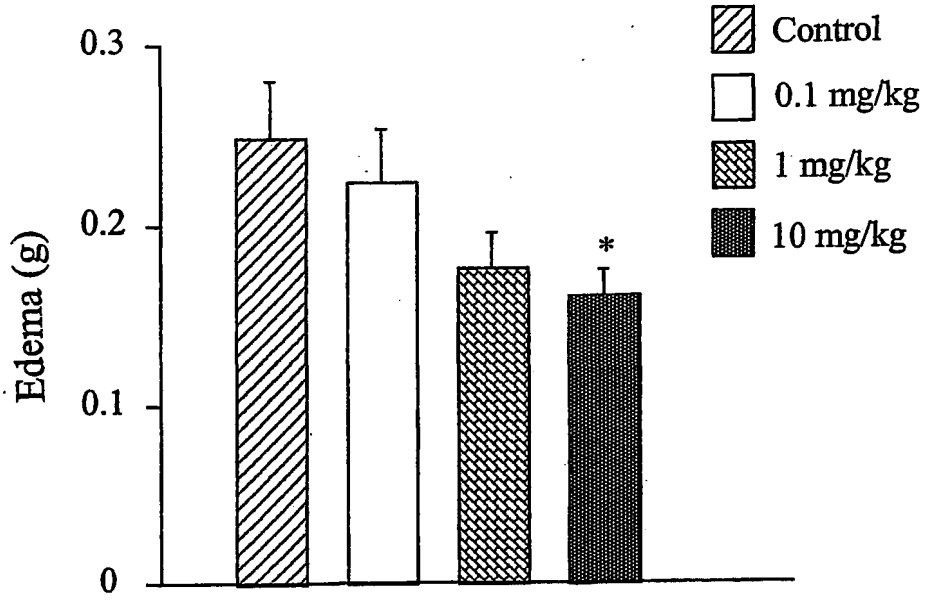
2.5
3.0
μM
Dextrosimendan
Levosimendan

FIG. 2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1 mg/kg
10 mg/kg
Edema (g)
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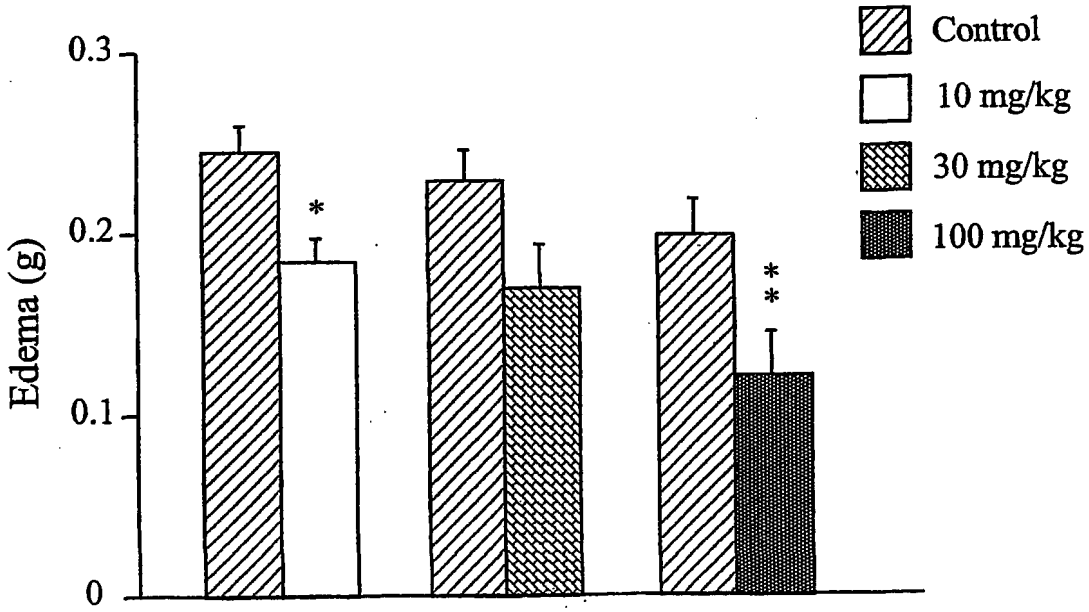
0.2
0.1
0
*

FIG. 3a


Control
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30 mg/kg
100 mg/kg
Edema (g)
0.3
0.2
0.1
0
*
**

FIG. 3b

INTERNATIONAL SEARCH REPORT

Int...nal Application No
PCT/FI 01/01000

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/50 A61K31/54 C07D285/16 A61P29/00 A61P11/06
A61P31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	DALIA M KOPUSTINSKIENE ET AL: "Levosimendan is a mitochondrial KATP channel opener" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 428, no. 3, 2001, pages 311-314, XP002902308 the whole document	1-10
X	JOUKO LEVIJOKI ET AL: "Further evidence for the cardiac troponin c mediated calcium sensitization by levosimendan: structure-response and binding analysis with analogs of levosimendan " J. MOL. CELL CARDIOL., vol. 32, 1 March 2000 (2000-03-01), pages 479-491, XP002902309 compound III, RN 274263-64-8	9,10
A		1-8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
15 February 2002	11 03. 2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gerd Strandell

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 383 449 A (ORION YHTYMAE OY) 22 August 1990 (1990-08-22) RN131741-39-4 page 13, line 30 - line 36; claims 1,2,7	9,10
A		1-8

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 01/01000

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-4 in part
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-4 in part

Present claims 1-4 relate to the use of any compound defined by reference to a desirable characteristic or property, namely capable of opening a mitochondrial Katp channel. Claims 1-4 cover the use of all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and / or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds (Compounds of formula (I)). In the present case, claims 1-4 so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, claims 1-4 also lack clarity (Article 6 PCT). An attempt is made to define the used compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely mainly those parts relating to use of the compounds according to claims 5-8. However, it is clear from the description that in claim 5 X must be "CH2 or S"

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established will not be the subject of an international preliminary examination (Rule 66.1(e) PCT). This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

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